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THE CONSTITUTION OF PROTOPLASM[1]

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AMONG the variety of elements which partake in the constitution of the cell, the nucleus is the largest single body and the one which has lent itself to the most successful investigation. The nucleus was seen as early as 1781 by Fontana, but it was not until the principles of the cell theory were established by Schwann, Remak and Virchow that its role in cell economy could take its full significance. With Flemming, Strasburger and van Beneden began a series of brilliant investigations on the nucleus, which culminated in the discovery of the phenomenon of mitosis and the demonstration of the unique role which the chromosomes assume in heredity. The success met with in the study of the nucleus was undoubtedly due to the circumstance that its structures were able to withstand the action of the fixatives which had come into use during the nineteenth century. This typical resistance of the nucleus to these agents and the nuclear affinity for basic dyes can in turn be traced to a substance present in abundance in all nuclei and segregated in the chromosomes during division, namely, thymonucleic acid.

The usual fixatives which had proved eminently suitable for the preservation of the nuclear framework destroyed the cytoplasmic structures, an effect due chiefly to the high concentration of acids and of alcohol which they contained. The artefacts so produced gave rise to erroneous views on the organization of protoplasm, such as the reticular and the froth theories. The outstanding advance in the study of cytoplasm came with the work of Altmann and his followers, who recognized the destructive action of acids and introduced bichromate as a fixative. This improve-

[1] Paper presented at the Gibson Island Conferences of the American Association for the Advancement of Science, Gibson Island, August 21, 1942.

ment in technique had the advantage of preserving most of the cytoplasmic inclusions and was responsible for the discovery of mitochondria. In the light of modern cytological studies, the cytoplasm appears to be essentially composite in nature, consisting of a continuous ground substance, the hyaloplasm, in which are found formed elements morphologically independent and varying widely in size and shape.[2] The morphology and distribution of mitochondria have extensively been studied and the conclusion is that these elements are constant constituents of cytoplasm. Secretory granules in animals and the plastids in plants are differentiated elements related to specialized functions of the cell and concerned with the elaboration of active substances as in the production of proteolytic enzymes in the pancreas, the production and storage of definite food materials such as starch, or the deposition of pigments. The Golgi body also appears to be a constant constituent of the cell, but its morphology, chemical composition and function are still obscure. The cytoplasmic elements just mentioned are large enough to be stained and studied by the usual cytological techniques. Their average diameter is appreciably greater than 0.2 μ, a value which represents approximately the limit in the power of resolution of the ordinary microscope. Visibility of minute objects within the cell can be considerably increased by means of intense lateral illumination as provided in the dark-field microscope. With the latter technique, it can be shown that the living cytoplasm, in addition to the "visible" inclusions, contains numerous highly refringent bodies of extremely small size, which may be at rest or in active Brownian movement. These ultramicroscopic bodies have escaped the attention of cytologists engaged in the study of fixed preparation, but have often been seen by students of living cells.[3] The chemical composition of the above cytoplasmic structures, their respective functions within the cell, their origin and the genetic relationship between the different classes of granules are problems which have not, and apparently can not be solved by purely microscopical techniques.

During the past few years, this laboratory has been engaged in the mechanical fractionation of normal and tumor cells by means of differential centrifugation, and purified fractions have been obtained from both nuclei and cytoplasm.[4,5,6] The first cell component to be isolated was a particulate substance of cytoplasmic origin which has been described in preceding papers under the provisional term, "small particles."[5] The present paper deals with a further study of this important cell constituent, together with a preliminary account of the isolation and analysis of zymogen granules from the liver and pancreas.[7] The position of the small particles in the organization of protoplasm and their possible relation to mitochondria and zymogen granules will be discussed.

Small particles: The method for the separation of the small particles has been described previously.[4,5] In this method, the cells are broken up and suspended in neutral water and the material is segregated and washed in a high-speed centrifuge. When the purified substance is concentrated in the centrifuge, it appears as a jelly-like pellet which is completely transparent. In this form, the material is not birefringent. Under transmitted light, the substance is somewhat amber in color, a property which is probably due to the large proportion of phospholipids which it contains. By reflected light, the color presented by the purified material may vary, depending on the tissue of origin. When the source of the particles is the liver, the color of the mass may be red or pink. It is usually light brown in chicken tumors and practically colorless in lymphoid tumors and in the pancreas. The unusually bright color exhibited by the liver fraction suggested that part of the purified material might have derived from the red corpuscles, since, in the liver, capillary blood may often form a large portion of the organ. For this reason, the work was repeated on livers which had been perfused prior to extraction. As regards color, yield and chemical composition (Table I), the results of this new series of experiments were identical with those already reported.[5] Therefore, it may be concluded that, in this case, the fraction under study had its origin in the hepatic cell.

When suspended in neutral water, the material forms opalescent preparations which, in the dark-field microscope, appear to be composed of extremely small bodies, highly refringent and in active Brownian movement. The size of the particles has been estimated to range approximately between 50 and 200 mμ in diameter, with no apparent segregation in definite size groups. The isolated particles have been shown to be complex formations in which a nucleoprotein of the ribose type occurs in association with a definite proportion of lipids, especially phospholipids.[4] The chemical composition of this cytoplasmic component is highly characteristic, as indicated by the consistent values obtained on chemical analysis and irrespective of the tissues from which it is prepared. Typical

[2] E. B. Wilson, "The Cell." The Macmillan Company, New York, 1925.

[3] R. Chambers, "General Cytology." The University of Chicago Press, Chicago, 1924.

[4] A. Claude, SCIENCE, 87: 467, 1938; *Proc. Soc. Exp. Biol. Med.*, 39: 398, 1938; SCIENCE, 90: 213, 1939; 91: 77, 1940.

[5] A. Claude, *Symposia on Quantitative Biology*, Cold Spring Harbor, 9: 263, 1941.

[6] A. Claude, *Trans. N. Y. Acad. Sciences*, Series II, 4: 79, 1942.

[7] Details of unpublished experiments, carried out with the collaboration of Dr. C. Auger, will appear in other journals.

values are close to 9 per cent. nitrogen and 1.5 per cent. phosphorus, except in embryos and pancreas, where the total phosphorus amounts to 2.1 per cent. The latter observation is of interest since embryonic tissues and pancreas have been found to be exceptionally rich in ribose nucleic acid. Tables I and II give the average values obtained on analysis of the small particles derived from rat and guinea pig liver (perfused) and from beef pancreas. Small particles of the type described above have been isolated from a great variety of tissues, and the value of 9 per cent. nitrogen appears to be representative for this class of cytoplasmic granules. A study of the available data indicates that the small particles are universal in distribution and that they represent a considerable portion of the cell (at least 10 to 15 per cent. by dry weight). The evidence suggests that the small particles are integral and, without doubt, important components of living protoplasm.

The position which the small particles occupy in the organization of the cell is of particular interest. This point has been under investigation in this laboratory for the past two years, not only with respect to the nature and role of the small particles, but also to the possible relation which may exist between them and other cytoplasmic structures. It was originally stated that the small particles might represent mitochondria or fragments of mitochondria.[4] This suggestion was based on apparent similarities in chemical constitution and on the estimate of the size of mitochondria, as found in the literature.[8] However, it can be shown that, as a rule, the width of mitochondria is appreciably greater than 0.2 μ, whereas the size range for the small particles, as found in our laboratory, appears to be roughly between 50 and 200 mμ in diameter; some particles are occasionally larger.[4] In the guinea pig liver, the red, small particles are definitely submicroscopic, although probably larger than our first estimate of 40 to 60 mμ in diameter.[5] In the spleen, pancreas and the liver of different species, the small particles have been found to be also submicroscopic. However, the sedimentation rate of the substance seems to be influenced by a number of factors, especially by the nature of the solvent and the pH of the solution and further study will be necessary before the actual size of the particles in different tissues can be ascertained. In rat leukemia, particles were found whose size was approximately that of the mitochondria, as seen in the living cells,[5] but a further study of rat leukemia extracts in the high-speed centrifuge showed that the protoplasm of the leukemic cells contained also, like that of other cells, a jelly-like substance composed of submicroscopic units.

[8] E. V. Cowdry, Carnegie Institution of Washington, *Contrib. Embryol.*, 8: 39, 1918.

The following observations on the intracellular segregation of cell constituents in high centrifugal fields indicate that, as a rule, the small particles do not derive from the visible elements of the cell but are undoubtedly part of the so-called ground substance. When hepatic or pancreatic cells are stained by the Altmann-Bensley technique, the zymogen granules and the mitochondria appear colored a vivid red against a diffuse background which contrasts by its slightly purple color. On the other hand, these various cell components can be forced to segregate within the cell by submitting a fragment of tissue to high-speed centrifugation. After 60 minutes at 18,000 × gravity, the different cell constituents are found segregated towards the centrifugal pole in the following order: the glycogen, the mitochondria and secretory granules, the "purple substance" and the Golgi body. The nucleus is at the level of mitrochondria and zymogen granules but above the glycogen. The upper surface of the "purple substance" appears as a straight line boundary. If the centrifugal force is sufficiently great, this boundary may be separated from the centripetal pole of the cell by an area which is clear and seemingly empty. This observation indicates that the apparently homogeneous ground substance contains a particulate, chromophilic component which dissociates itself from the true hyloplasm under moderately high centrifugal force. This "purple substance" which can thus be demonstrated in the cell by the combined techniques of staining and high-speed centrifugation constitutes probably the source of the small particles. This is indicated by the fact that the same color differentiation can be obtained *in vitro,* by staining the isolated fractions, namely, small particles and secretory granules, on the same slide and by the same technique. In this case, the substance of the small particles takes a purple color against the red color of the secretory granules. Staining the tissues with the Regaud technique leads to similar observations, where the sedimentable component of the ground substance (small particles) can be identified by a gray-blue color contrasting with the blue-black color of the secretory granules and mitochondria. Thus, the evidence, so far, indicates that the mass of the small particles does not derive from the grossly visible elements of the cell but constitutes a hitherto unrecognized particulate component of protoplasm, more or less evenly distributed in the fundamental substance and which impart to it, in well-preserved preparations, its staining properties. In order to differentiate the small particles from the other, already identified elements of the cell, it may be convenient in the future to refer to this new component under a descriptive name which would be specific. For this purpose the term *microsome* appears to be the most appropriate. The term microsome, meaning

small body, was applied originally by Hanstein (1880) to any granules, as seen in living protoplasm. The use of the word was progressively narrowed down, being retained as a general term to designate any small granules of undefined nature.[2] Under these conditions, it seems proper to suggest that the term microsome, already familiar to cytologists, should be restricted to designate the small particles exclusively.

Zymogen Granules: The technique for the separation of secretory granules from guinea pig liver has been described in another paper.[5] A new series of experiments on the perfused liver of guinea pigs and the liver of normal rats indicates that the results obtained with this method are highly reproducible, as shown by the very close values obtained on chemical analysis, even in two different species of animal (Table I). Extreme variations in individual experiments were less than 1 per cent. for the nitrogen, less than 4 per cent. for the phosphorus values. Twelve per cent. nitrogen and 1.25 per cent. phosphorus, or values very close to these figures, have been obtained consistently in recent experiments and it may be concluded that they constitute characteristic features of the liver secretory granules. These granules are readily separated from the other liver components, and neutral water can be used in their preparations. In the centrifuge, the liver granules form a loose sediment which is opaque and presents a buff color which resembles that of compressed yeast.

TABLE I

FRACTIONATION OF THE LIVER BY DIFFERENTIAL CENTRIFUGATION: CHEMICAL COMPOSITION OF SMALL PARTICLES AND OF SECRETORY GRANULES. (AVERAGE VALUES FROM 2 EXPERIMENTS)

Animal species	Fraction	N per cent.	P per cent.	C per cent.	H per cent.	S per cent.	Amount obtained (dry weight) per cent.
Guinea Pig	Small Particles	9.08	1.69	56.03	8.23	0.7	7.5
	Secretory Granules	12.08	1.26	54.55	8.09	0.82	4.6
Rat	Small Particles	9.14	1.62	55.44	8.26	0.68	10.0
	Secretory Granules	12.09	1.25	54.45	7.91	0.94	6.6

Separation and purification of zymogen granules from pancreas have presented much greater difficulties, due especially to the presence of a powerful lipase which rapidly attacks the lipid portion of the microsomes and that of the zymogen granules—an action which results in the destruction of their structure and which leads eventually to the denaturation of their proteins. An adequate technique was finally worked out, the details of which will be given in a later paper. This technique is based on a time centrifugation of 30 minutes at 2,000 × gravity. The pancreatic granules so obtained are rapidly destroyed in water, dissociating into a particulate component and an insoluble, highly colored substance. They are fairly well preserved in 0.8 per cent. NaCl solutions at pH 7.5. In the centrifuge, the zymogen granules form a loose and opaque sediment. The color of the material is characteristically yellow and often yellow-green. The chemical composition of the zymogen granules is strikingly similar to that of the liver secretory granules. This resemblance is especially apparent when comparing the results of analysis which are summarized in Tables I and II. In both cases, the value for nitrogen is equal to, or approaches 12 per cent. Moreover, it can be seen that in both liver and pancreas the small particles on the one hand, the secretory and zymogen granules on the other hand, have similar respective values. In both organs, the secretory or zymogen granules have a higher nitrogen and sulfur content, but a lower phosphorus, carbon and hydrogen content than the corresponding small particles. In their gross chemical composition, therefore, the secretory granules, whether from liver or pancreas, are fundamentally alike. The similarity of their elementary structure suggests that these granules represent differentiated members of a single class of cytoplasmic organs which are built on an identical framework, in spite of the specialized and exclusive functions which they may be called upon to perform in organs as dissimilar as the liver and the pancreas.

TABLE II

FRACTIONATION OF BEEF PANCREAS BY DIFFERENTIAL CENTRIFUGATION: CHEMICAL COMPOSITION OF SMALL PARTICLES AND ZYMOGEN GRANULES. (AVERAGE VALUES FROM 5 EXPERIMENTS)

Fraction	N	P	C	H	S
Small Particles	9.16	2.11	57.88	9.06	0.46
Zymogen Granules ...	11.94	1.88	50.39	7.82	0.69

Relation between Microsomes, Mitochondria and Secretory Granules: The studies reported above indicate that, on the basis of general physical properties and elementary chemical composition, there exist two definite classes of cytoplasmic elements, namely, the microsomes and the secretory granules. On the other hand, it has been shown previously that small particles and secretory granules are chemically related, both being complex formations composed of phospholipids and ribonucleoproteins associated in characteristic proportions.[4,5] These findings raise the important problem of the origin of the particulate components of cytoplasm and that of the possible developmental relationship which may exist between the microsomes and the other cytoplasmic structures. The secretory granules from guinea pig liver and from beef pancreas disintegrate spontaneously, when kept

distilled water, leaving a residue composed of particles which form jelly-like pellets in the centrifuge and which, on analysis, were found to contain about 9 per cent. nitrogen. Thus, the secretory granules seem to contain a substance physically and chemically similar to the so-called "small particles." This observation may suggest that the secretory granules develop from the microsomes or that they have a common origin.

In 1934, Bensley and Hoerr isolated from the liver of guinea pigs a fraction referred to by them as mitochondria.[9] From its physical characteristics the fraction of Bensley and Hoerr seems to correspond to our liver secretory granules. However, inasmuch as the chemical analysis previously reported by these authors is different from our findings, it is impossible to know at the moment whether the two fractions are really identical. Secretory granules are abundant in the guinea pig liver, especially in the fasting animal, where they accumulate and seem to fill the cell completely, and it appears probable that up to the present, mitochondria have not been isolated in a pure or concentrated form, a large part of the so-called "mitochondria" fraction representing probably, to a large extent, mature secretory granules.

Nucleic Acids and Cell Structures: One point which may be discussed in the light of the new findings is that of the origin of the granular substance of cytoplasm. The following considerations suggest that the distribution of nucleic acids in the cell is intimately connected with this problem. Thymonucleic acid has been shown to be exclusively a nuclear constituent. More precisely, it constitutes the distinctive substance of chromosomes. Thanks to the Feulgen technique, it has been possible to show that thymonucleic acid is found nowhere except in the nucleus and that it is present equally in nuclei of animals and plants as well as in homologous formations of more primitive cells such as yeast and bacteria.

Ribose nucleic acid, a close relative of thymonucleic acid, has been known for some time to occur in animal cells. Caspersson and Schultz have shown recently that it is a constituent of nucleoli.[10] Work in this laboratory brought attention to the fact that ribonucleic acid in the cytoplasm is localized on particulate or granular structures. This was first demonstrated for the small particles[4] and more recently for the secretory[5] and zymogen granules. This observation assumes exceptional significance if we consider the fact that, so far, any organic structure which has been found to possess directly the property of self-duplication has also been shown to contain nucleic acid of the one or the other type. The outstanding example is the chromosome. The relation is even more striking when the self-perpetuating unit is not a complex structure but a simple substance such as the autocatalytic nucleoprotein of Stanley. The crystallized viruses of plants are nucleoproteins. Other viruses which have been successfully purified have proved to have a nucleoprotein as a major constituent. This is the case for the Shope papilloma virus.[11] The agent causing Chicken Tumor I has been shown to depend on the integrity of a nucleoprotein for its activity.[12] It appears unlikely that nucleic acid represents no more than an inert substrate whose main purpose is to hold the structure together, as it has often been suggested to be the case in the chromosome. In the light of modern research, it seems probable that nucleic acid plays a fundamental role, perhaps of an enzymatic nature, in the process which enables the structure to reproduce itself.

In the process of cell division, the duplication of chromosomes can be followed under the microscope. There is evidence that the centrioles and certain plastids in plants are reproduced by auto-division.[2] De Vries attempted to show that this was also the case for the tonoplasts. Outside of these isolated cases, there is no satisfactory explanation to account for the perpetuation of cytoplasmic structures, particularly for the increase in granular substance, which must necessarily take place at each mitotic division. Two mechanisms for the perpetuation of these structures are possible: either each element has the power to reproduce its own species or it is being produced by an outside agency which, itself, must be self-perpetuating. The findings that the small particles or microsomes and the secretory granules contain ribonucleic acid suggest that these cytoplasmic constituents, like the other nucleic acid-containing structures, may be endowed with the property of self-duplication. The latter assumption, which should be no more than a working hypothesis, offers a biochemical basis for the view that each vital element which contributes actively to the life of the cell has the power to reproduce its kind. Except for the plant plastids, the experimental proof that other differentiated cytoplasmic granules reproduce in this manner have been elusive and it has often been suggested that these granules are formed *de novo* in the ground substance. The existence of a reservoir of self-perpetuating microsomes from which the specific granules may develop would provide a satisfactory answer to this problem but much research will be needed before this point can be clarified. If our hy-

[9] R. R. Bensley and N. L. Hoerr, *Anat. Rec.*, 60: 449, 1934; R. R. Bensley, *Anat. Rec.*, 69: 34, 1937.

[10] T. Caspersson and J. Schultz, *Proc. Nat. Acad. Sciences*, 26: 507, 1940.

[11] J. W. Beard, A. R. Taylor, D. G. Sharp and D. Beard, *Surgery, Gynecology and Obstetrics*, 74: 509, 1942.

[12] A. Claude and A. Rothen, *Jour. Exp. Med.*, 71: 619, 1940.

pothesis regarding the mode or origin of the microsomes is correct, then these small particles would share with the cell itself, and within the cell, with the chromosomes, the centrioles, the plastids and possibly the tonoplasts, the most general law of living matter, that of genetic continuity. It must be emphasized that the above conception is concerned exclusively with the biochemical aspect of the origin and evolution of the granular substance of the cytoplasm. It does not deny the possibility that the cytoplasmic constituents may come, in the course of their evolution and activity, under the influence of the nucleus.

THE UTILIZATION OF AQUATIC FOOD RESOURCES

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THE food and forage situations in Europe during the past three years have stimulated discussions regarding the availability of certain aquatic plants and animals not now generally used as sources of such material. The utilization of large aquatic plants as forage for animals and the use of both marine and fresh-water plankton as sources of human food have been mentioned. Little has been said, however, about the quantity of these materials found in fresh waters, and a brief consideration of this phase of the problem may be worth while.

Large aquatic plants have been used as forage for cattle in Yugoslavia for many years,[1] and it has recently been reported that they are now being used extensively for the same purpose in Sweden owing to the scarcity of fodder in that country. While these plants have a rather high mineral content (10 to 35 per cent. ash), they contain considerable quantities of nutritious materials; protein makes up 12 to 25 per cent. of the dry weight, fat 1 to 3 per cent. and the remainder of the organic matter consists of carbohydrates, of which crude fiber constitutes 16 to 21 per cent. Using the averages of these percentages of organic matter and assigning 4 calories to each gram of protein and of carbohydrate and 9 calories to each gram of fat, their energy value is about 1,450 calories per pound, dry weight. A mean of 18.5 per cent. of the dry plants consists of crude fiber and the greater part of this may be regarded as indigestible; deducting this part of the carbohydrate would leave an energy value of 1,100 calories per pound for the digestible organic matter in the plants.

Rather large crops of these plants are found in some of the Wisconsin lakes; in Mendota, for example, the annual yield has been estimated at 2,100 tons of air-dry material, or about one ton per acre of the shallow area in which they grow.[2] In Green Lake the crop was estimated at 1,600 pounds per acre, air-dry, in the shallow water zone and the total crop at 1,528 tons. In the soft-water lakes of northern Wisconsin, the yields of large aquatics are much smaller, ranging from 10 to 100 pounds per acre in the vegetated zones.

With respect to the use of plankton for human food, Clarke[3] has discussed this problem from a marine standpoint, referring especially to the plankton crustacea, while Hardy[4] and other authors have called attention to the possibility of using fresh water as well as marine plankton for food; both phytoplankton and zooplankton have been mentioned in some of the communications. It has been pointed out that the chief difficulty is to obtain enough plankton material to warrant the labor involved in collecting it. The smaller organisms which make up the great bulk of the plankton are especially difficult to capture. One author has suggested the use of the tons of plankton collected on the filter beds of cities that filter their water supplies, while others have considered various types of nets. The latter capture only the larger organisms, chiefly zooplankton forms, which usually constitute not more than 10 per cent. of the total plankton and frequently as little as 5 per cent.

Data obtained on Wisconsin lakes show that the dry organic matter of the plankton found in them ranges from a minimum of half a gram in the soft-water lakes to a maximum of 9 grams per cubic meter in some of the hard waters. This minimum in Crystal Lake represented a standing crop of 45 kilograms per hectare (41 pounds per acre), while the maximum in Lake Waubesa indicated a standing crop of 966 kilograms per hectare, or 862 pounds per acre; the live weight of this dry organic matter would be ten times as large, since 90 per cent. or more of the weight of the living organisms consists of water. The mean standing crop of plankton in Lake Waubesa over a period of two years was 242 kilograms per hectare, dry weight, or 216 pounds per acre, of which 49 per cent. consisted of protein, 5 per cent. fat and the

[1] Vilim Mršić, SCIENCE, 83: 391, 1936.
[2] H. W. Rickett, *Trans. Wis. Acad. Sci.*, 20: 501, 1921, and 21: 381, 1924.
[3] SCIENCE, 80: 602, 1939.
[4] *Nature*, 147: 695, 808, and 148: 115, 143, 314, 375, 1942.

remainder was made up of various carbohydrates, including 6 per cent. pentosans and 4 per cent. crude fiber.

Just how much of this plankton material could be harvested and still leave a sufficient number of the organisms to perpetuate the crop and supply sufficient food for larger organisms has not been determined. Likewise the rate of turnover in this standing crop of plankton can not be definitely assessed because it includes a large variety of forms, ranging from bacteria and algae to crustacea and insect larvae, which are diverse in size and in rates of reproduction; in addition growth, multiplication and destruction of the constituent organisms takes place throughout the year. Under favorable conditions, bacteria may multiply several times a day, while algae and protozoa are probably limited to once or perhaps twice a day; the life span of the crustacea ranges from about a week to three months or more, depending chiefly on temperature and food conditions, and that of insect larvae may extend to 8 months or more. Assuming a turnover in this heterogeneous crop of plankton once a month during the year, which is a conservative estimate especially during spring, summer and autumn, would give an annual yield of 2,892 kilograms of dry organic matter per hectare, or 2,580 pounds per acre. It seems probable that the actual annual production is more nearly twice the above amount.

From the standpoint of collecting this plankton, it was found that at least 98 per cent. of it could be obtained by passing the water through a large clarifier type of centrifuge at a rate of 1.5 cubic meters in two hours. The average yield from samples of this size in Lake Waubesa was approximately 5 grams of dry organic matter per cubic meter of water. Assuming the same values for protein, fat and carbohydrate as noted for the large aquatics, the energy value of these 5 grams of plankton would be 20 calories. Thus with an energy requirement of 3,000 calories per person per day, it would take the plankton from 150 cubic meters of water to satisfy this energy demand. To obtain the plankton from this amount of water would require the operation of the centrifuge continuously for a period of 200 hours, or a little more than 8 days, to satisfy the energy required for one day. From this result it is evident that the installation of a large battery of these centrifuges in order to reduce the time of obtaining the desired quantity of this material would not be a profitable investment.

Another difficulty may be mentioned in connection with certain forms included in the phytoplankton and protozoa. While both marine and fresh-water crustacea have been pronounced as "not unpleasant" by those who have eaten them, it seems probable that the verdict would not be so favorable if the smaller plankton organisms were included in the menu because a number of them produce odors and tastes[5] that are not only unpleasant but quite disagreeable under certain conditions. Fresh-water plankton crustacea make up such a small percentage (less than 10 per cent.) of the total crop of plankton that they can not be relied on to contribute greatly to the energy requirement of a person, but they might be used to supplement a sub-standard food ration to a certain extent. They have a high food value, since an average of 52 per cent. of their dry weight consists of protein and 13 per cent. fat. One of these crustaceans, namely Daphnia, is cultured extensively in pools and ponds by fish culturists for food for young fish and there is no apparent reason why they can not be grown in quantities large enough to serve as a supplementary food for man, especially during the more favorable growing seasons in spring, summer and autumn. They are readily preserved for future use by the simple process of drying.

The plankton, either directly or indirectly, makes an important contribution to the food supply of fish; in fact, the menu of fish in one way or another is derived principally from the plankton, the bottom flora and the bottom fauna. Fish, however, are very poor converters of the biota of a lake into nutritious food for man in the form of their own bodies; they are much more easily harvested and much more palatable to man. Their inefficiency as converters is shown by the fact that they constitute less than 3 per cent. of the total weight of the biota in some of the smaller lakes.

As indicated above a turnover once a month in the plankton crop of Lake Waubesa would give an annual yield of 2,592 pounds per acre of dry organic matter, or 25,920 pounds per acre of live organic matter. In control seining on this lake carried out by the Conservation Department, the average annual yield of carp from 1934 to 1939, inclusive, was 278 pounds per acre;[6] in addition the estimated catch of game and pan fish by anglers was 17 pounds per acre in 1938 and 1939, thus making the average fish yield 295 pounds per acre for these six years. This annual yield of fish was only 1.1 per cent. of the estimated annual production of live plankton as indicated above; in other words only one pound of fish per acre was produced annually for every 88 pounds of plankton. It must be remembered also that the bottom flora and fauna are not taken into account in this comparison; if they were included the result would be still more unfavorable for the fish. The weights of these two groups of organisms have not been determined so

[5] G. W. Whipple, "The Microscopy of Drinking Water," New York, 1927.

[6] D. G. Frey, Ph.D. Thesis. 1940.

that no definite ratio can be given for the total biota; the bottom flora and fauna, however, are major sources of food for the fish, especially the larger sizes, while plankton is the chief source during the first two years of life. With such a large surplus of plankton, it seems probable that 50 per cent. of it could be harvested for human food, if desirable and practicable, without decreasing the rate of fish production.

In spite of the fact that the annual production of fish appears unusually low in comparison with the other biological resources of Lake Waubesa, it compares very favorably with the beef production of pasture land, for example, excellent pasture is required to produce 200 to 300 pounds of beef per acre per year. It may be pointed out also that the fish yields in 1938 and 1939 were more than 500 pounds per acre in this lake, with a maximum of 550 pounds per acre in 1939. The latter yield is approximately twice as large as the maximum beef production of first-class pasture land.

OBITUARY

WILLIAM ALBERT SETCHELL

WILLIAM ALBERT SETCHELL, professor emeritus of botany of the University of California, died in Berkeley on April 5, 1943. Had he lived ten days longer he would have reached his seventy-ninth birthday. Professor Setchell was born in Norwich, Connecticut, on April 15, 1864. He graduated from Yale University with the degree of A.B. in 1887. He then entered Harvard University for graduate study and received the degrees of A.M. and Ph.D. at that institution in 1888 and 1890, respectively. He was appointed instructor in biology at Yale in 1891 and remained in that position until 1895, when he was called to a full professorship and headship of the department of botany of the University of California; this he held until his retirement in 1934, after which he became professor emeritus.

In 1920 Dr. Setchell was married to Mrs. Clara Ball Caldwell, who died on September 4, 1934.

Professor Setchell enjoyed membership in several professional societies, but in addition he was honored by election to several organizations of special distinction. He was a fellow of the American Association for the Advancement of Science, of the American Academy of Arts and Sciences, the California Academy of Sciences and the Torrey Botanical Club. He was a member of the National Academy of Sciences, the American Philosophical Society and the Washington Academy of Sciences in this country, and of several distinguished societies abroad. Among these latter were Société Biogéographie, Société Linnéenne de Lyon, Botanical Society of Japan, the Linnaean Society of London and the Kunglig Vetenskaps och Vitterhets Samhället i Göteborg.

In the field of science to which he devoted his life Setchell made a distinguished record. Thoroughly competent though he was in botanical taxonomy in general, his distinction lay in his monumental contributions to algology and especially to marine algology. From the cooperative researches which he carried on through most of his life with the late Professor Nathaniel Lyon Gardner, there resulted in published form several large volumes on the marine algae which are among the most thoroughgoing and impressive in the world. Moreover, he was never a narrow student of taxonomy. He was as much interested in the causes of the geographic distribution of algae as in their orderly classification, and his contributions to our knowledge of the rôle of temperature in the distribution of algae have received world-wide notice. Setchell was one of the early students of plant genetics in this country and inaugurated the fundamental genetical studies on Nicotiana which have since been carried on with distinction by Professors Goodspeed and Clausen.

His versatility in his field of science was paralleled by his general versatility. With the classical background of his college training he combined a flair for writing and speaking in graceful and humorous vein, thus making him a companion sought after by circles of laymen as well as of scientists. His appreciation and critical appraisal of the best in literature and music went far beyond that of most laymen. Through his possession of so many and varied qualities of mind and spirit he gained numerous friends in Europe and in other continents which he visited on several occasions. These friends regarded him with affection as well as respect. Likewise, in this country his friends were legion and he was especially gifted in appealing to young men from every biological field who always surrounded him in numbers. Many a young man in biological work in this country received inspiration and material aid from him, as well as wise counsel and lasting friendship.

Those of us who knew Professor Setchell intimately not only admired his hearty personality, fine learning and expertness with the marine algae, but in addition regarded him as an example of the best in American scholarship and manhood. He was a great algologist, a sturdy American and a loyal and devoted friend. All who knew him will mourn his loss to us.

CHAS. B. LIPMAN

DEPARTMENT OF BOTANY,
UNIVERSITY OF CALIFORNIA

RECENT DEATHS

DR. JAMES EWING, professor of oncology at the Cornell University Medical College and consulting pathologist at Memorial, Roosevelt and New York Hospitals, from 1913 to 1939 director of Memorial Hospital, died on May 16 at the age of seventy-six years.

EDWARD A. WHITE, professor emeritus of floriculture and ornamental horticulture at Cornell University, died on May 13 at the age of seventy years.

DR. CLARA E. SMITH, professor of mathematics at Wellesley College from 1924 until her retirement in 1934, died on May 12. She was seventy-eight years old.

DR. J. LEON LASCOFF, past president of the American Pharmaceutical Association, died on May 4 at the age of seventy-six years.

DR. ALEXANDER P. ANDERSON, botanist and industrial chemist, who maintained a private laboratory at Red Wing, Minn., died on May 7 at the age of eighty years.

DR. WARRINGTON YORKE, F.R.S., Alfred Jones professor of tropical medicine in the University of Liverpool and at the Liverpool School of Tropical Medicine since 1929, died on April 24 at the age of sixty years.

SCIENTIFIC EVENTS

THE FUTURE OF FOOD PRODUCTION IN GREAT BRITAIN

A REORGANIZATION of the British Ministry of Agriculture which would include the setting up of a statutory body, on the lines of the Forestry Commission, for food production and control, free from political controversy, is recommended, according to *The Times*, London, in a report issued by a special committee appointed by the Royal Agricultural Society of England to consider post-war policy.

The members of this committee were Sir Arthur Hazlerigg (chairman), Lord Mildmay of Flete, Lord Cranworth, Sir Merrik Burrell, Sir Roland Burke, Sir George Courthope, M.P., Sir Archibald Weigall and A. H. B. Talbot-Ponsonby. The statutory body, they suggest, should be appointed by the Minister of Agriculture, who would be responsible for it to Parliament. Its main duties would be: (1) To deal with the present work of the Food Ministry; (2) to function as an Imports Board; (3) to stabilize prices and link guaranteed prices to guaranteed wages; and (4) to make sure that the land is farmed well and that the fertility of the soil is not only maintained but in many cases materially increased.

The report urges that, after a complete survey of the land, a definite acreage should be earmarked and set aside for agriculture, and that, so long as this land is so earmarked, no death duties should be levied on it. Land-owners and farmers would naturally have to submit to more control than hitherto under ordinary peace-time conditions.

The committee proposes for each county a special committee with one or more paid executive officers, who would travel round the county and report to their committee, which would deal drastically with cases of bad farming. The committees would have to be carefully chosen from the best landowning and farming interests, and there must be a right of appeal to an impartial tribunal of experts in farming and members with some legal experience.

The change would entail the repeal of part, if not all, of the Agricultural Holdings Act, 1923, and county councils would need new agricultural committees, which would still deal with small-holdings, diseases of animals and agricultural education.

In the reconstruction of the Ministry of Agriculture, provision would have to be made for a recruitment of a special branch of the Civil Service having practical experience of farming. As a first measure the committee recommends that five surveyors of food production, drawn from the ranks of those who have themselves farmed successfully, should be appointed to the staff of the ministry to be graded as first-grade civil servants commanding high salaries.

The whole basis of entry into the ministry and promotion, it is suggested, should be reorganized, and almost every entrant should undergo training to include at least one year's practical work on a farm. He should either take a degree in agriculture at a university or a two-year course at any leading agricultural college, where, after passing an examination such as for a national diploma in agriculture, he could graduate into the ministry.

NEW FELLOWS OF THE ROYAL SOCIETY OF EDINBURGH

IT is announced in *Nature* that the following have been elected ordinary fellows of the Royal Society of Edinburgh: Dr. A. T. Andreasen, principal of the Orissa Medical School, India; A. H. R. Ball, rector of the Royal High School, Edinburgh; J. G. Chalmers, department of chemistry, University of Edinburgh; J. B. Crawford, treasurer of the Bank of Scotland, Edinburgh; Dr. R. G. M. Dakers, Heriot-Watt College, Edinburgh; the Right Hon. William Y. Darling, Lord Provost of the City of Edinburgh; the Right Hon-

orable John Dewar, Baron Forteviot of Dupplin; N. Dobson, Ministry of Agriculture's Veterinary Laboratory, Weybridge, Surrey; Dr. A. Dunbar, Edinburgh; Dr. H. R. Fletcher, government botanist, Edinburgh; Professor R. Fürth, Dewar research fellow, University of Edinburgh; Professor J. H. Gaddum, professor of materia medica, University of Edinburgh; Professor A. C. Hardy, regius professor of natural history, University of Aberdeen; W. B. Hislop, Edinburgh; J. D. Imrie, City Chamberlain, Edinburgh; the Right Hon. Thomas Johnston, Secretary of State for Scotland; D. K. Kevan, Secretary, Ministry of Supply (Timber Control), Edinburgh; Dr. Robert Kirk, Kitchener School of Medicine, Khartoum; C. C. Learmonth, secretary, Merchant Company, Edinburgh; Professor C. H. Lobban, professor of civil engineering, King's College, University of London; Robert Lyon, principal, Edinburgh College of Art; W. W. McClelland, executive officer to the National Committee for the Training of Teachers; G. MacKenzie, general manager, British Linen Bank, Edinburgh; Colonel G. H. G. McLean, Glasgow; Duncan Macnaughton, Edinburgh; Dr. G. C. McVittie, King's College, University of London; Dr. D. M. Morison, Royal Hospital for Sick Children, Edinburgh; Dr. Charles Ockrent, Glasgow; Dr. J. M. Robertson, Gardiner professor of chemistry, University of Glasgow; Dr. W. M. Smart, regius professor of astronomy, University of Glasgow; Dr. W. J. Stuart, consulting surgeon, Royal Infirmary of Edinburgh; J. M. Thomson, secretary, Scottish Education Department; Dr. E. Warhurst, Heriot-Watt College, Edinburgh; Dr. T. S. Westoll, department of geology, University of Aberdeen; Dr. R. W. Wheldon, department of agriculture, University of Durham; H. H. Wood, department of English literature, University of Edinburgh.

THE FOUR HUNDREDTH ANNIVERSARY OF THE DEATH OF COPERNICUS

ADDRESSES by prominent educators, as well as a musical program, will feature exercises which the University of Pennsylvania will conduct in memory of Nicholas Copernicus, the Polish astronomer, in the Irvine Auditorium, Thirty-fourth and Spruce Streets, at 3:30 o'clock on Sunday afternoon, May 23.

The exercises, which will be open to the public, will commemorate the four hundredth anniversary of the death of Copernicus and of the publication of his epochal treatise, "De Revolutionibus Orbium Coelestium." It was in this treatise that Copernicus revolutionized man's concept of his relation to the universe by first developing the theory that the earth was not the center of the universe but revolved around the sun.

Dr. Thomas S. Gates, president of the University of Pennsylvania and a member of the Copernican Quadricentennial National Committee, will preside over the ceremonies and there will be addresses by Dr. Lynn Thorndike, professor of history at Columbia University, and Dr. Charles W. David, professor of history at the University of Pennsylvania.

Selections by the Paderewski Polish Choral Society, under the direction of Dr. Walter Grigaitis, will follow each address, and members of the society in Polish costume will serve as ushers at the exercises.

The Reverend Francis Palecki, rector of St. Hedwig's Church, will give the invocation, and the Reverend J. Clemens Kolb, chaplain of the University of Pennsylvania, will deliver the benediction.

The exercises at the university will form part of a nation-wide tribute to the memory of Copernicus.

In addition to President Gates, members of the Copernican Quadricentennial National Committee of the University of Pennsylvania include Dr. A. Newton Richards, vice-president of the university in charge of medical affairs, and Dr. John R. Kline, professor of mathematics and secretary of the American Mathematical Society.

THE DEPARTMENT OF EXPERIMENTAL BIOLOGY OF THE AMERICAN MUSEUM

THE reorganization of the Department of Experimental Biology of the American Museum of Natural History has been announced by the administration. The name has been changed to the Department of Animal Behavior, and the scientific staff of the department is constituted as follows: Dr. Frank A. Beach, *Chairman and Curator;* Dr. T. C. Schneirla, *Associate Curator;* Lester R. Aronson and Dr. Albert P. Blair, *Assistant Curators;* Miss A. Marie Holz, *Scientific Assistant;* Dr. Libbie H. Hyman, Dr. William Etkin and Dr. Charles M. Breder, Jr., *Research Associates.*

The twofold function of the department is defined as research in animal behavior and the planning of exhibits on the same subject. The orientation of the department's research program, involving a coalescence of field and laboratory methods of investigation, deals with general principles revealed in the behavior of various animal groups. The current investigational program includes studies on invertebrates, fishes, amphibians, birds and mammals. At present a large part of the research of the department is centered about problems of reproductive behavior, and the assistance of the Committee for Research in Problems of Sex, National Research Council, is greatly facilitating this series of studies.

Plans for exhibits designed to illustrate broad principles of animal behavior and to emphasize the evolu-

ion of major reaction patterns have been approved. Such exhibits enrich the visitor's concept of the psychobiological aspects of animal life and increase his perspective and understanding of human behavior.

THE ELECTROCHEMICAL SOCIETY AND THE KILGORE BILL

THE following resolution was adopted unanimously by the Electrochemical Society at its eighty-third meeting, held in Pittsburgh from April 8 to 10:

WHEREAS, It appears that enactment of the Kilgore-Patman Bill S-702, HR2100 for the establishment of an Office of Scientific and Technical Mobilization

(a) Would confuse the war effort by creating at this time a new agency for the direction of the scientific and engineering program which is now so effective in the prosecution of the war and

(b) Might develop in peace-time a gigantic bureaucracy which would impede scientific and technical progress, be it

Resolved, Therefore, that members of the Electrochemical Society be urged to examine this bill and communicate their views on it to their congressmen, and furthermore be it

Resolved, That the Electrochemical Society in convention assembled, express its general opposition to the enactment of any measure which embodies government supervision, regimentation and control of the scientific and technical resources of the nation in peace-time.

THE AMERICAN ACADEMY OF ARTS AND SCIENCES

AT the annual meeting of the American Academy of Arts and Sciences, held on May 12 at its house, 28 Newbury Street, Boston, the election of twenty-seven fellows was announced:

MATHEMATICAL AND PHYSICAL SCIENCES

Bradley Dewey, Dewey and Almy Chemical Company, Cambridge.
Enrico Fermi, professor of physics, Columbia University.
Philipp Frank, lecturer on physics and mathematics, Harvard University.
Edwin Powell Hubble, astronomer, Mount Wilson Observatory, Pasadena, Calif.
Edwin Herbert Land, president, Polaroid Corporation, Cambridge.
Cecilia Payne-Gaposchkin, astronomer, Harvard College Observatory.
Donald Charles Stockbarger, associate professor of physics, the Massachusetts Institute of Technology.
Hugh Stott Taylor, professor of chemistry, Princeton University.

NATURAL AND PHYSIOLOGICAL SCIENCES

Arlie Vernon Bock, professor of hygiene, Harvard University.
David Bruce Dill, professor of industrial physiology, Harvard University.
Chester Scott Keefer, professor of medicine, Boston University.
Lewis Don Leet, associate professor of geology, Harvard University.
Brenton Reid Lutz, professor of biology, Boston University.

SOCIAL SCIENCES

Augusta Fox Bronner (Mrs. William Healy), director, Judge Baker Guidance Center, Boston.
Ada Louise Comstock, president, Radcliffe College.
Benjamin Morris Selekman, associate professor of business administration, Harvard University.
Payson Sibley Wild, Jr., associate professor of government, Harvard University.
Charles Edward Wyzanski, U. S. district judge for Massachusetts.

THE HUMANITIES

Leonard Bacon, poet and teacher.
Willa Cather, novelist.
Carleton Stevens Coon, associate professor of anthropology, Harvard University.
Angus Dun, dean, Episcopal Theological School, Cambridge.
Hugh O'Neill Hencken, curator of European archeology, Harvard University.
Perry Gilbert Eddy Miller, associate professor of history and literature, Harvard University.
Jean-Joseph Seznec, associate professor of Romance languages and literature, Harvard University.
Randall Thompson, composer and teacher.
Thornton Niven Wilder, novelist and dramatist.

The officers elected for the year 1943–44 were:

President, Harlow Shapley.
Vice-Presidents, Percy W. Bridgman, S. Burt Wolbach, Sidney B. Fay and Fred N. Robinson.
Corresponding Secretary, Abbott Payson Usher.
Recording Secretary, Hudson Hoagland.
Treasurer, Horace S. Ford.
Librarian, Frederick H. Pratt.
Editor, Robert P. Blake.

The Academy voted to award the Rumford Medals to Charles Edward Kenneth Mees, of the Eastman Kodak Company, for his contributions to photography.

SCIENTIFIC NOTES AND NEWS

THE doctorate of science was conferred on May 9 at the commencement exercises of Syracuse University on Dr. William M. Smallwood, professor emeritus of zoology of the university, and on Dr. Charles Hurd, professor of organic chemistry at Northwestern University.

ST. LAWRENCE UNIVERSITY, Canton, N. Y., conferred at commencement an honorary degree on Dr. Leonard Carmichael, president of Tufts College, formerly professor of psychology at Brown University and at the University of Rochester.

DR. HENRY F. JOHNSTONE, professor of chemical engineering at the University of Illinois, was presented at the thirty-fifth semi-annual meeting on May 10 with the award of the American Institute of Chemical Engineers. The medal is awarded annually for "an outstanding contribution to chemical engineering literature within a three-year period." It was presented by James G. Vail, chairman of the award committee. The citation described as of "exceptional merit" papers read by Professor Johnstone on heat transfer and distillation before recent meetings of the institute.

DR. CHARLES F. WILINSKY, executive director and superintendent of the Beth Israel Hospital, Boston, chief medical officer of the Boston Public Safety Committee, was presented on April 12 with the annual medal of the Boston City Club for distinguished civic service, in recognition of "the outcome of his work in organizing the medical section of the city's civilian defense effort, and for his work during the Cocoanut Grove disaster." This gold medal is presented each year to the citizen adjudged by the club to have "rendered the most outstanding civic service to greater Boston."

THE Clarke Memorial Medal for 1942 has been awarded by the council of the Royal Society of New South Wales to Dr. W. L. Waterhouse, of the University of Sydney, for "outstanding contributions in the sphere of natural science, particularly in plant pathology."

THE fellowship award of $1,000 of Sigma Delta Epsilon has been made to Dorothy Marie Ziegler to further her work at the Barnard Free Skin and Cancer Hospital, St. Louis, on changes in epidermal cells, comparing harmless and malignant cells through the application of improved new techniques. The work is being carried on under the direction of Dr. Edmund V. Cowdry, of Washington University.

THE American Association of University Women has made twelve grants to conduct research projects under $1,500 fellowship awards for 1943–44. Among those receiving awards in the sciences are Harriett F. Mylander, of Baltimore and Cambridge, to complete a scientific study of central inhibition; Elly M. Jacobsen, of the University of California at Los Angeles, research in the physiology of reproduction; Dr. Elizabeth Z. Burkhart, of Clarksville, Ark., experiments in endocrinology, and Dr. Dorothy I. Parker, botanist of Bargersville, Ind., to write the second volume of a botanical encyclopedia of the United States.

IT is reported in *Nature* that at the annual meeting of the British Institution of Chemical Engineers, on April 2, the following medals for 1942 were presented: *Osborne Reynolds Medal,* L. O. Newton; *Moulton Medal,* W. K. Hutchison and Dr. E. Spivey, for their paper on "Design and Performance of Cooling Towers"; *Junior Moulton Medal and Award,* Dr. S. H. Wade, for his paper on "Evaporation of Liquids in Currents of Air"; *William Macnab Medals,* J. H. Sharp and F. J. Wilkins.

DR. E. W. SMITH has been elected president of the British Institute of Fuel for the session 1943–44. He will take office in October.

PRESTON S. MILLAR, president of the Electrical Testing Laboratories, has been elected president of the New York Electrical Society. Dr. Colin G. Fink, professor of electrochemistry at Columbia University, has been elected first vice-president.

H. E. ROBINSON, assistant chief chemist of Swift and Company, Chicago, has been made president of the Chicago Chemists Club.

PROFESSOR H. H. KNIGHT, of the department of zoology of the Iowa State College, was elected on May 6 president of the college chapter of Sigma Xi.

DR. DAVID W. E. BAIRD, JR., acting dean, has been appointed dean of the Medical School at Portland of the University of Oregon. He succeeds Dr. Richard B. Dillehunt, who has resigned.

DR. GEORGE D. SCARSETH, who has been serving as professor of soils and as soil chemist at the Experiment Station of Purdue University, has been appointed head of the department of agronomy, effective on July 1. He has been a member of the department since 1937 and succeeds Professor A. T. Wiancko, who is retiring on June 30 after serving for forty years. Eric W. Stark, of the Texas State Forest Service, has been appointed associate professor of forestry in the School of Agriculture and associate in forestry and conservation in the Experiment Station. For the past three years, he has served as chief of the Division of Forest Products Research. He will carry on research and teaching in wood properties and wood utilization.

P. I. DEE has been appointed professor of natural philosophy at the University of Glasgow.

DR. MAURICE L. TAINTER, professor of pharmacology at Stanford University and at the College of Physicians and Surgeons, San Francisco, has been named research director of the Winthrop Chemical Company. His headquarters will be at Rensselaer, N. Y.

DR. T. SMITH TAYLOR, formerly professor of physics, in charge of the Graduate School of the Newark College of Engineering, has become chief of selenium rectifier development with the Federal Telephone and Radio Corporation at East Newark.

PROFESSOR HARVEY BRACE LEMON is on leave of absence from the University of Chicago. He has become chief physicist at the Ballistics Research Laboratory, Aberdeen Proving Grounds, for the duration of the war.

DR. MARGARET D. CRAIGHILL, dean of the Woman's Medical College of Pennsylvania, has leave of absence to enable her to accept a commission of major in the division of preventive medicine in the Surgeon General's Office. She will specialize in preventive medicine in the Women's Army Auxiliary Corps.

DR. E. RAYMOND HALL, Guggenheim fellow, University of California at Berkeley, returned on May 2 after two and a half months spent in Mexico, where he made ethno-zoological studies in the field. While in Mexico he gave illustrated lectures at the Instituto de Salubridad y Enfermedades Tropicales and at the Benjamin Franklin Library on the results of his biological studies in Michoacan and on the Latin American fellowships offered by the University of California.

SIR HAROLD HARTLEY has been appointed general treasurer of the British Association as from April 1, the beginning of a new financial year. He succeeds Professor P. G. H. Boswell, who has resigned after twelve years' service in office, first as a general secretary (1931–35), and then as general treasurer (1935–43).

IT is reported in the *Times*, London, that the British Ministry of Agriculture, the Department of Agriculture for Scotland and the British Ministry of Information have asked a party of four agriculturists with practical experience of the food production campaign to visit the United States and Canada in the near future. The party will consist of T. R. Ferris, executive officer of the Dorset War Agricultural Executive Committee; Watson Jones, vice-chairman of the Shropshire War Agricultural Executive Committee; T. B. Manson, Divisional Land Officer of the Department of Agriculture for Scotland; and A. G. Street, farmer and author. They will tour the United States and Canada, giving lectures on the British farmers' war effort. The visit is expected to last for two to three months.

RICHARD P. STRONG, Colonel, M.C., A.U.S., director of tropical medicine at the Army Medical School, Washington, D. C., delivered the Leo Loeb Lecture at Washington University Medical School, St. Louis, on April 29. The problems of the war regarding malaria, bacillary dysentery, filariasis and typhus fever were especially discussed. On April 30 at the School of Medicine of St. Louis University he delivered an address upon plague.

DR. ERNEST CARROLL FAUST, professor of parasitology and head of the department of tropical medicine of the School of Medicine of Tulane University, delivered the third series of Ernest A. Sommer Memorial Lectures at the Medical School of the University of Oregon, Portland, from May 17 to 22. The first lecture was entitled "Horizons of American Tropical Medicine"; other lectures were on "Insects as Agents and Transmitters of Disease," "Malaria," "Yellow Fever and Dengue," "Amebiasis" and "Filariasis."

DR. CARL J. WIGGERS, professor and director of physiology at the Western Reserve University Medical School, has recently given the following lectures: "The Irreversibility Characteristic of Shock," before the Detroit Physiological Society on March 18; "The Value of Adrenal Cortex Preparations in Hemorrhagic Shock," Michigan Academy of Science Shock Symposium on March 26, and "Experimental Approaches to the Shock Problem," Adam Miller Lecture at the Long Island Medical College, Brooklyn, N. Y., on April 13.

PROFESSOR J. EDWARD HOFFMEISTER, of the department of geology of the University of Rochester, gave a public lecture on April 22 on "The Importance of Geology in Military Strategy in the Pacific Campaign." This was the second in a series of popular scientific lectures sponsored by the university chapter of the Society of the Sigma Xi. These lectures were initiated to acquaint the public with modern scientific facts of present-day importance. The first lecture of this series was given by Professor J. R. Murlin, of the university, on January 22. He spoke on "Food Rationing and the Nutritional Welfare of Our People."

PROFESSOR CARL O. DUNBAR, director of the Peabody Museum, Yale University, gave the address following the annual dinner of the Sigma Xi Club of the University of Connecticut on April 22.

A SERIES of six lectures is being given under the auspices of the New York Institute of Finance on Mondays, at 3:45 o'clock, in the Governors' Room of the New York Stock Exchange. The lecturers include John Mills and Dr. K. K. Darrow, of the Bell Telephone Laboratories, and Dr. Willard F. Libby, of the University of California.

IN the issue of SCIENCE for April 23, Dr. Foster Kennedy was referred to as professor of neurology at the College of Physicians and Surgeons of Columbia

University. Dr. Kennedy is professor of neurology in the Cornell University Medical College.

A MEETING of the American Physical Society, including invited and contributed papers, will be held at Stanford University, Calif., on July 10.

DR. T. R. HOLLCROFT, associate secretary of the American Mathematical Society, reports that the three hundred ninety-fifth meeting of the society was held at Hunter College, New York City, on April 24. The attendance was about two hundred, including one hundred and forty-three members. The following addresses were given by invitation of the program committee—"Spectral Theory," by Professor Nelson Dunford, of Yale University, and "Absolutely Convergent Trigonometric Sums," by Professor R. H. Cameron, of the Massachusetts Institute of Technology. There were two sessions at which thirteen contributed papers were presented. Ten additional papers were read by title. The excellent arrangements made by the department of mathematics of Hunter College were very much appreciated by all attending the meeting.

PROFESSOR H. J. VAN CLEAVE writes: "The general seminar in the department of zoology and physiology of the University of Illinois has devoted two meetings per month through the current year to the history of zoology in some of the leading American universities. In most instances a full hour has been given to each of the more important institutions with a former student or staff member from that institution in charge of the program. In the aggregate these programs have given a fairly comprehensive sketch of biology in America."

A GIFT of $43,500 from the Rockefeller Foundation has been made to Columbia University in support of three years' research on problems of intermediate metabolism in the department of biochemistry.

THE Paleontological Research Institution of Ithaca, N. Y., has recently been presented by Mrs. C. S. Bentley, of Plattsburg, N. Y., with a collection of recent sea shells mainly obtained from the West Coast though with genotype representatives from other oceanic regions.

DR. C. C. LITTLE, director of the Roscoe B. Jackson Memorial Laboratory at Bar Harbor, Maine, has announced a grant of $35,000 to the laboratory from the trustees of the Rockefeller Foundation. This grant is for a five-year period beginning on July 1, and is a contribution toward the expenses of establishing and maintaining a mammalian stock center. According to Dr. Little the money will be used primarily in connection with the work at the Hamilton Station in Salsbury Cove. It is hoped that in the five-year period a good beginning may be made in the establishment and maintenance of stocks of rabbits, rats and guinea pigs for use in scientific experimentation. Work has already been under way for some time at the Hamilton Station. It is hoped that the scientific results obtained will be of value not only in cancer research but to experimental medicine as a whole.

DISCUSSION

"MOCK DOMINANCE"

IN a recent issue of SCIENCE,[1] Richey points out that a hybrid from two plants, one with twice as many internodes of half the length of the other, would have a greater height than either parent, providing the hybrid internode number and length were each the arithmetical mean of those of the parents. For such gene interaction resulting in heterosis in height he suggests the term "mock dominance" which he considers not to be dominance in its genetic sense. I believe further comment is necessary to clarify the issue.

(1) If height can be taken as a statistical creation compounded of two fundamental elements (internode length and number), then Richey's conclusions and terminology are justifiable. One might as logically, however, consider height and internode length as fundamental and their quotient, internode frequency, a compound. It should be noted in this connection that, in an actual cross, the factors would not necessarily interact in the manner postulated by Richey.

(2) If a particular gene substitution always makes the same contribution to the total effect, gene interaction is said to be absent. If the contribution is not always the same but depends merely on the total effect of the residual genes, the scale may be transformed into one on which each factor has the same effect throughout the range.[2] Interaction that can be thus eliminated by the use of a transformed scale may conveniently be termed "statistical interaction."

In other cases the effect of a gene substitution depends not merely on the total effect of the residual genes but also on the particular genes producing this total effect. That this is the case in the example proposed by Richey will be apparent from a consideration of the following list of genotypes and the relative

[1] F. D. Richey, SCIENCE, 96: 2490, 1942.

[2] See, for example, S. Wright, *Jour. Amer. Statist. Assoc.*, p. 163, 1926.

plant heights resulting from the gene action which he postulates:

nndd	1
nnDd, Nndd	1.5
NNdd, nnDD	2
NnDd	2.25

The substitution of N for n in a genotype which would otherwise produce a plant 1.5 units in height gives a genotype producing a plant either 2 or 2.25 units in height, depending on the residual genes present. Interaction of this type can not be made to disappear by transformation of scale and is non-"statistical" in the sense defined above. In this particular example it can be thought of either as complementary (inter allelic) or dominance (intra allelic) interaction. Only non-statistical interaction can ever lead to heterosis in the offspring of two equal parents with respect to the measure considered.

It is doubtful whether non-statistical interaction should be described as "mock" regardless of the measure involved even though the existence of gene interaction based on certain measures might be relatively insignificant from the standpoint of analysis of gene action or of practical application.

(3) If the action of any particular gene substitution affecting internode number or length were proportional to the total effect of all the genes present, the height of the hybrid in Richey's example would equal that of the two parents. In such case the logarithms of height, internode number and internode length would all constitute scales on the basis of which interaction is absent. Probably no other type of simply expressed gene action can result in the absence of non-statistical interaction for measurements related to each other as products, quotients and powers, as are lengths, areas, volumes and many shape indices. This constitutes a statistical reason for expecting more frequently an approximation toward independent action of gene differences when the action is expressed as logarithms of measures of these types than when expressed as the measure themselves or any other simple function of them.

EVERETT R. DEMPSTER

DIVISION OF GENETICS,
UNIVERSITY OF CALIFORNIA

A NEW GROWTH FACTOR FOR STREPTOCOCCUS LACTIS

USING as standard a sample of folic acid concentrate (7.7 per cent.) kindly supplied by Dr. R. J. Williams we compared the amount of folic acid[1] and norite eluate factor[2] in various types of extracts and liver preparations and found that some of these materials are much more active for *Streptococcus lactis R* than for *Lactobacillus casei*. In contrast an extract of spinach had the same degree of activity for both organisms.

These differences can be demonstrated to be due to the presence of another substance which we have now isolated. The new substance effectively replaces the folic acid standard in the case of *S. lactis* but is inactive for *L. casei*. We have calculated that 1γ of this product has the same potency for *S. lactis* as 56γ of the folic acid standard but that the same amount of this factor is less active than 0.0004γ of the folic acid standard for *L. casei*.

We believe that this newly isolated substance, for which we have reserved the designation of a name until its chemical nature is determined, is not folic acid or the norite eluate factor but a new growth factor.

JOHN C. KERESZTESY
EDWARD L. RICKES
JACOB L. STOKES

RESEARCH LABORATORIES,
MERCK AND COMPANY, INC.,
RAHWAY, N. J.

SULFAGUANIDINE OR SULFA-AMIDINE?

INCONSISTENCIES or inaccuracies in nomenclature are fairly common in the field of chemistry. The offense to students is perhaps not serious when such practice involves unusual cases. This does not, however, justify an attitude of indifference in the matter of accuracy whether it be in naming compounds or in the use of scientific terminology. Attention is called here to the misnaming of one of the sulfa drugs. The names and formulas of the more common and useful of these compounds are to be found in most recent editions of books on chemotherapy or biochemistry. An acquaintance with the parent compound and the modifying groups would enable any one to write the formulas of such compounds as sulfathiazole, sulfapyridine or sulfadiazine. To apply the same technique in the writing of the formula for sulfaguanidine would lead to obvious error. In the interests of accuracy this substance should be named sulfa-amidine or, for those who desire a more euphonious name, sulfamidine.

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CLASS DISTINCTION AMONG AMERICAN MEN OF SCIENCE

IN several preceding editions of the Biographical Directory of American Men of Science, one thousand

[1] Folic acid was determined by means of the *Streptococcus lactis R* assay method of Mitchell, Snell and Williams. (*Jour. Am. Chem. Soc.*, 63: 2284, 1941.)

[2] Norite eluate factor assays using *Lactobacillus casei* (B. L. Hutchings, N. Bohonos and W. H. Peterson, *Jour. Biol. Chem.*, 141: 521, 1941) were made in essentially the same medium as for folic acid assays.

were differentiated from the rest by means of a star attached to their names and designated the "leading men of science." It is now proposed to continue this class distinction in a new edition of the directory.

I do not know of any useful purpose that has been served by the formation of a superior class of scientists, but I do know that it has created no end of ill feeling among those who have been excluded. Moreover, if it is useful to "star" one thousand and designate them the "leading men of science," why would it not be useful to "double star" five hundred of these as super leaders and "triple star" one hundred as super, super leaders, etc.?

It seems to me that in a democracy class distinction should everywhere be discouraged as much as possible and that there should be no fixed differentiation into classes in any group of individuals without the sanction of the group. I therefore suggest that the continuation of "starring" of scientists in the directory be put to a vote of those involved.

S. O. MAST

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SCIENTIFIC BOOKS

LIGHT

Chemical Aspects of Light. By E. J. BOWEN. 191 pages. New York: Oxford University Press. January, 1943. $4.00.

THIS little book covers a wide range of subject-matter and is "intended only for the student who, whether by youth, age or other cause, is not equipped to participate freely in the mathematical struggles by which formal and quantitative solutions of problems are obtained." It is addressed therefore to those who, not equipped to make new advances themselves, "wish to know something of a branch of contemporary science." Even with mathematics at a minimum, both youth and age will find the book hard reading in places, probably by reason of the great compression of material in the text. The first chapter on waves and matter, 32 pages long, has paragraphs on linearly, circularly and elliptically polarized waves, the electromagnetic theory of Maxwell, the electronic theory of matter, interference, diffraction, resolving power of optical instruments, the electron microscope, lenses, double refraction or birefringence, fluorescence, optical activity, strains in materials, liquid crystals, streaming double refraction in colloidal systems, Tyndall light scattering, depolarization, reflection, absorption and transmission, dispersion and refraction, the photo-electric effect, Rayleigh scattering, glossy and matt surfaces, color of pigments and nephelometry. It makes a concentrated diet for any reader.

Ten chapters follow the first and expand some of the topics. Chapter 3, with 47 pages on the absorption and emission of light, is a good summary of atomic and molecular spectra. Succeeding chapters treat fluorescence, luminescence of solids, photochemical reactions, photosynthesis (perhaps the evidence from radioactive carbon should have been included in this), the photographic process (a brief, compact survey of the essentials in 8 pages), the reactions of the retina, photo-cells and chemiluminescence. There are 17 pages of appendices on light filters, photochemical technique and phosphors. There are three pages of bibliography and a Table of Constants. In this latter the value for the velocity of light in vacuo $= 2.99796 \times 10^{10}$ cm per sec, should be, according to Birge, 2.99776. If youth and age find the book difficult reading the trained chemist, not specialist in this field, can find here a trustworthy summary of the present state of the science. The format, printing, paper and binding of the book are a tribute to the Clarendon Press in the third year of total war.

HUGH S. TAYLOR

EMBRYOLOGY

The Embryological Treatises of Hieronymus Fabricius of Aquadependente. The Formation of the Egg and of the Chick (De Formatione Ovi et Pulli). The Formed Fetus (De Formato Foetu). A facsimile edition, with an introduction, a translation and a commentary. By HOWARD B. ADELMANN. Ithaca, N. Y.: Cornell University Press. xxiv + 883 pp. 46 plates. 1942. $12.50.

JEROME FABRIZIO, born at Aquadependente, was professor of anatomy at Padua from 1565 to 1613. In this chair he was the third of the distinguished successors of Andreas Vesalius. His importance as a teacher is sufficiently attested by the fact that his greatest pupil, William Harvey, not only obtained one of the most important clues for his discovery of the circulation of the blood from Fabricius's description of the valves of the veins, but also founded his lifelong studies of embryology upon those of his master.

Fabricius himself was the first since the time of Aristotle to study embryology from a comparative point of view. Through his lectures and his two books on animal development he raised embryology to the rank of an independent science. The first of these books, that on the formed fetus, appeared in 1604; the second, which deals with the embryology of the chick, was published after his death, in 1621. In spite of their importance, neither was ever translated into any modern language, and it is now more than

two hundred years since they were last published in Latin. Through the devoted labor of Professor Adelmann these books, the foundation stones of modern embryology, are now set before us in a noble volume which contains the two Latin texts in facsimile, with English translations which are both readable and scholarly, entertaining biographical notes and instructive commentaries, copious annotations and cross-references and a detailed bibliography.

The studies of Fabricius were of course made without the microscope. They concern the structure of the reproductive organs of the hen, the structure of the egg and the way in which the embryo is laid down. The observations on the mammalian fetus concern almost exclusively the placenta, membranes and fetal blood vessels. As Professor Adelmann points out, the ultimate goal of Fabricius, as of Aristotle and Galen, was "to explain causes, and particularly to elucidate the final cause, the end or purpose served by each part." Structure and function were studied primarily for their aid in the comprehension of the end or useful purpose. These two books therefore are couched in a tone of scholastic inquiry which requires (and receives) a good deal of explanation by the translator in order to make them clear to the present-day reader. In his introductory chapters, Adelmann traces the previous history of embryology from Aristotle through Galen and the sixteenth century writers, including Vesalius and Coiter. Then, in a careful analysis of the text of Fabricius, he shows us how the latter began his work saturated with the spirit and point of view of Aristotle and Galen and how he had to adjust his observations of fact to the doctrinal patterns of his times.

There has been a tendency to over-emphasize the traditionalism and the factual errors of Fabricius. He made several striking mistakes, such as deriving the chick from the chalazae of the egg; but these are completely outweighed by a host of careful and (for the time) accurate descriptions of the egg and the chick, of the mammalian placenta and membranes and of the umbilical and fetal vessels. He studied a very wide range of species, and was the first to describe and illustrate in print the diffuse placenta of the pig and horse and the human decidua. The illustrations which accompany his texts are remarkably clear and instructive, and many of them could still be used for teaching. They are well reproduced in this volume.

The reviewer has perhaps said enough to indicate that Dr. Adelmann has provided much more than reprints and translations of these books. He has shown us their proper place in the history of embryology and has made it possible for students in our day to understand the achievement of their author.

Students of Harvey will find here a careful study of the relations between his work and that of Fabricius. In the translations, all the more important passages which Harvey quoted from Fabricius are specially indicated.

This work, from its touching Latin dedication to the memory of Dr. Adelmann's mother and sister, through to its excellent index, is a monument of scholarship—learned, thorough and withal interesting, and satisfyingly complete. Students of embryology and of the history of science, now and in the future, will be grateful not only to the author, but also to Cornell University, the Council of Learned Societies and the Carnegie Corporation, for making its publication possible. Special mention should be made of the handsome format, and of the typography designed by Robert Josephy, which combines beauty and legibility with a clever suggestion of seventeenth century style, making the English translations and the commentaries appear fully compatible with the dignified Paduan printing of the Latin texts.

GEORGE W. CORNER

SPECIAL ARTICLES

CURARE ALKALOIDS FROM CHONDODENDRON TOMENTOSUM

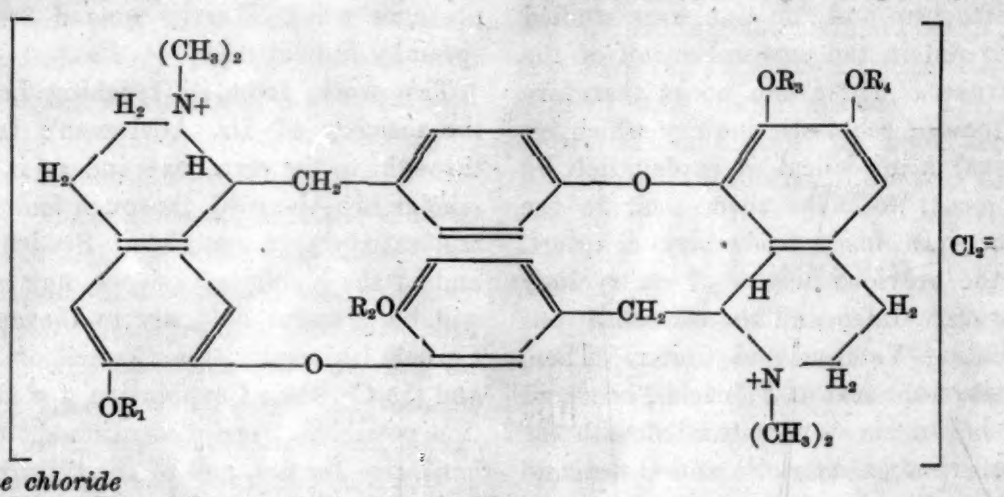
CURARE is the generic name for a group of highly effective arrow poisons of plant origin used by the South American Indians. Recent clinical work has given encouraging indications that this drug, with its powerful lissive action on the voluntary musculature, might become a valuable therapeutic agent in the treatment of spastic paralysis, for moderating the convulsions in the shock-therapy of certain psychoses, and as an adjunct to anesthesia in surgery. So far, the chief obstacle to the therapeutic use of curare has been the widely varying potency and the uncertain origin and composition of the available preparations.

The isolation of a physiologically active, crystalline alkaloid from curare proved to be a difficult task. After numerous unsuccessful attempts by other workers, H. King, in 1935, finally announced the isolation of a crystalline, highly active quaternary base chloride, designated by him d-tubocurarine chloride, from a specimen of tube curare.[1] The earlier work of M. Scholtz, of E. Spaeth and of F. Faltis on the inactive tertiary base, l-curine from curare, and the related alkaloids bebeerine and isobebeerine (isochondodendrine) found in the drug *pareira brava,* enabled King to establish the structure of d-tubocurarine chloride as that of a bisbenzylisoquinoline alkaloid in which the nitrogen atoms are quaternary (formula I). On the

[1] H. King, *Jour. Chem. Soc.* (London) 1381, 1935.

basis of a subsequent chemical investigation of pot curare[2] and of the tertiary alkaloids from various menispermaceous plants[3] this author expressed the belief that the still unsettled problem of the botanical provenance of tube- and pot-curare would eventually be solved by an examination of the N. O. Menispermaceae and particularly of the genus *Chondodendron*.

The problem of identifying the botanical species employed by the Indians of the Amazon region in the preparation of curare has been admirably clarified by the work of Krukoff and Moldenke.[4] Their definitive study of the American Menispermaceae leaves little to be desired in the way of botanically correlating the various species used as ingredients. They list as important in this respect: *Abuta imene, Chondodendron polyanthum, Ch. limaciifolium, Ch. tomentosum, Ch. ignitanum, Ch. candicans, Telitoxicum minutiflorum, T. peruvianum* and *Abuta rufescens,* all menisperms, and also several *Strychnos* species.



I. *d-Tubocurarine chloride*
$R_1 = CH_3$; $R_2 = H$; of R_3 and R_4, one is H, the other CH_3.
II. *d-Chondocurine dimethochloride*
$R_1 = CH_3$; $R_2 = H$; of R_3 and R_4, one is H, the other CH_3, but in arrangement which is the reverse of that in I.
III. *d-Tubocurarine dimethylether iodide*
$R_1 = R_2 = R_3 = R_4 = CH_3$; anion $I^{=}_2$ instead of $Cl^{=}_2$.

The authenticated plant material collected by Krukoff was investigated chemically and pharmacologically by Folkers.[5] Later, Folkers and Unna[6] reported on the chemical examination of Chazuta curare and its botanical components. As with other species, the crude extract obtained from the dried stem bark of *Chondodendron tomentosum* proved to be highly toxic to frogs and failed to elicit the typical curare response. After separation of the alkaloids into quaternary and non-quaternary fractions, the former caused the characteristic curare symptoms in frogs but was toxic to a cat. The authors, commenting on the close resemblance of the action of this fraction from *Chondodendron tomentosum* to that of native Peruvian curare, cite this fact as supporting evidence for the statement of Krukoff that this plant is the chief ingredient. Folkers was also careful to point out that the Indians extract green fresh bark, whereas the laboratory tests were made with dried bark, and that this may account for the essentially negative results.

On the other hand, the essential ingredients of calabash curare are almost certainly not menispermaceous plants, but members of the *Strychnos* family. This follows from the work of Wieland and collaborators,[7] who isolated from calabash curare several highly active quaternary bases chemically unrelated to the bisbenzylisoquinoline alkaloids, and later demonstrated the presence of some of these compounds in the bark of *Strychnos toxifera*.

We have had the opportunity to examine a sample of curare, prepared by Indians of the upper Amazon, in which only one plant species, namely *Chondodendron tomentosum,* was used. The plant species was identified by a botanist at the time of preparation and authenticated by herbarium specimens. We have been able to isolate from this curare, by procedures which will be described in detail elsewhere, four crystalline tertiary bases and a highly active crystalline quaternary base, which was shown to be identical with the d-tubocurarine of King. In terms of physiological activity the yield of the quaternary alkaloid was 40 per cent.

The tertiary bases, three of which (1, 3 and 4 below) represent isomers of the formula $C_{36}H_{38}O_6N_2$, are:

(1) d-Isochondodendrine, a phenolic alkaloid previously obtained by Scholtz[8] from *pareira brava* and by King[3] from various other *Chondodendron* species.

[2] H. King, *Jour. Chem. Soc.* (London) 1472, 1937.
[3] H. King, *Jour. Chem. Soc.* (London) 737, 1940.
[4] B. A. Krukoff and H. N. Moldenke, *Brittonia,* 3: 1, 1938.
[5] K. Folkers, *Jour. Am. Pharm. Assoc.,* 27: 689, 1938.
[6] K. Folkers and K. Unna, *Arch. Int. Pharmacodyn.,* 61: 370, 1939.
[7] H. Wieland *et al., Ann.* 627: 160, 1937; 536: 68, 1938; 547: 140, 156, 1940.
[8] M. Scholtz, *Arch. Pharm.,* 251: 136, 1913.

(2) d-Isochondodendrine dimethylether, an alkaloid encountered so far only in an asiatic Menisperm, *Cissampelos insularis*.[9] (3) A new alkaloid for which we propose the name *d-chondocurine*. By N-methylation this compound was converted into amorphous quaternary halides (chloride and iodide) which differed chemically and in physiological activity from the corresponding halides of d-tubocurarine. However, on methylation of the phenolic groups in addition to N-methylation it yielded a crystalline dimethylether dimethiodide which was found to be identical with d-tubocurarine dimethylether iodide (III). It must therefore be concluded that d-chondocurine corresponds to d-tubocurarine in regard to the basic ring skeleton and the configuration of the asymmetric centers, but differs from it besides in the valency of the nitrogen atoms, by the arrangement of methylated and free phenolic hydroxyl groups (II). It is noteworthy that the as yet unknown tertiary base, ("d-tubocurine"), corresponding in *all* respects to d-tubocurarine has so far not been encountered by us in *Chondodendron tomentosum* in spite of the relative abundance of the quaternary base in this plant. (4) A new levorotatory alkaloid, differing from l-curine, the tertiary base previously found in curare by Boehm[10] and isolated by King and others from extracts of various *Chondodendron* species. The new alkaloid yielded a crystalline dimethiodide and an amorphous dimethylether dimethiodide. Pending the preparation of larger amounts the question of its chemical relationship to the other alkaloids of this group will have to be left open. There was no evidence for the presence of either l-curine or its enantiomorph, d-bebeerine, in our extract.

In Table 1, the properties of the isolated alkaloids as well as of the quaternary bases and the quaternary dimethylethers prepared from them are recorded. The potency of d-tubocurarine chloride measured by the rabbit head drop method of Holaday,[11] is 6.5 units per mg.[12] The same value is obtained for the (amorphous) iodide of this base after correction for the different atomic weight of the anion. The finding that the quaternary derivative of d-isochondodendrine is practically devoid of lissive action is confirmatory of earlier reports.[13] The more surprising is the fact that the quaternary base derived from d-chondocurine (either in the form of the chloride or the iodide) possesses about three times the lissive potency of d-tubocurarine. Also the crystalline quaternary base corresponding to alkaloid 4 is only slightly less potent than d-tubocurarine. This is, to our knowledge, the first instance where tertiary alkaloids of the bisbenzylisoquinoline type have been shown to yield quaternary bases approximating or exceeding in physiological potency the active constituents of native curare.

TABLE 1

ISOLATED AND DERIVED ALKALOIDS FROM CHONDODENDRON TOMENTOSUM

Tertiary alkaloids	Quaternary alkaloids
d-Isochondodendrine* m.p. 300°; $[\alpha]_D$ + 120° (0.1N HCl)	d-Isochondodendrine dimethiodide m.p. 280°; $[\alpha]_D$ + 87° (water). < 0.4 units per mg.
d-Isochondodendrine dimethylether* m.p. 270°; $[\alpha]_D$ − 15° (chloroform)	d-Isochondodendrine dimethylether dimethiodide m.p. 300°; $[\alpha]_D$ − 7° (ethanol). 1.6 units per mg.
d-Chondocurine* m.p. 234°; $[\alpha]_D$ + 200° (0.1N HCl)	d-Chondocurine dimethiodide ("d-Chondocurarine iodide") amorphous; $[\alpha]_D$ + 178° (methanol). 20 units per mg. dimethylether identical with d-tubocurarine dimethylether iodide.
Alkaloid 4* m.p. 167°; $[\alpha]_D$ − 248° (0.1N HCl)	Dimethiodide of Alkaloid 4 m.p. 250°; $[\alpha]_D$ − 135° (methanol). 5 units per mg. Dimethylether dimethiodide of Alkaloid 4 amorphous 18 units per mg.
Tertiary alkaloid corresponding to d-tubocurarine ("d-tubocurine") unknown.	d-Tubocurarine chloride* m.p. 275°; $[\alpha]_D$ + 225° (water). 6.5 units per mg. d-Tubocurarine dimethylether iodide m.p. 266°; $[\alpha]_D$ + 160° (water). 60 units per mg.

* Alkaloids isolated from *Chondodendron tomentosum*; the other compounds are derivatives prepared in the laboratory. The standard errors for the potency figures given lie within a range of ± 2 to 3 per cent.

The unexpected finding that methylation of the free phenolic hydroxyl groups in all the quaternary bases markedly increased the physiological activity is likewise of interest. In the case of d-tubocurarine, this increase is about nine-fold, and with d-chondocurine dimethiodide, which yields the same dimethylether, three-fold. A similar enhancement of potency (about four-fold) results from the O-methylation of the dimethiodide of alkaloid 4 and, on a considerably lower level of activity, of d-isochondodendrine dimethiodide. O-ethylation of d-tubocurarine has no such marked effect (diethylether iodide, 10 units per mg), while

[9] H. Kondo, M. Tomita and S. Uyeo, *Ber. Dtsch. Chem. Ges.*, 70: 1890, 1937.

[10] R. Boehm, *Abh. Kgl. sächs. Ges. Wiss.*, 22: 203, 1895; 24: 23, 1896; *Arch. Pharm.*, 235: 660, 1897.

[11] H. Holaday, to be published.

[12] The unit referred to its equivalent to 1 mg of an arbitrary curare standard preparation, which was later shown by us to contain likewise d-tubocurarine as the active principle. The potency figures for the other compounds listed in Table 1 were arrived at by comparison with this standard or with crystalline d-tubocurarine chloride. We wish to emphasize that the relative potencies thus determined hold true only when the rabbit is employed as the test animal. When d-tubocurarine dimethylether iodide was compared with the unmethylated base by the same technique in other species (monkey, mouse, dog) the ratios deviated considerably from that obtained in the rabbit. These findings as well as the data incorporated in this paper will be reported in detail by Holaday and associates in a separate communication. We wish to express our sincerest thanks to Mr. H. Holaday of the Biological Laboratories of E. R. Squibb and Sons for placing the bioassay data at our disposal.

[13] M. Scholtz, *Arch. Pharm.*, 252: 513, 1914.

O-butylation renders the quaternary base practically inactive.

In conclusion, we wish to point out that the availability of pure crystalline preparations with high curare activity will fill an urgent need for well-defined material for physiological and clinical experimentation.

SUMMARY

Crystalline d-tubocurarine has been isolated in good yield from curare prepared from a single plant species, namely, *Chondodendron tomentosum*. This result establishes with certainty the botanical origin of this compound and substantiates the supposition that it is this species which furnishes the active constituent in certain types of curare.

The extract from this plant furthermore yielded two new tertiary alkaloids which could be converted into physiologically active quaternary bases.

Methylation of the phenolic hydroxyl groups in the quaternary bases resulted in a 3–9-fold increase in physiological potency.

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THE IN VITRO EFFECT OF INSULIN IN PIGEON BREAST MUSCLE[1,2]

IN 1938 Krebs and Eggleston[3] demonstrated an *in vitro* oxidative effect of insulin on a suspension of minced pigeon breast muscle in phosphate buffer to which has been added certain oxidizable substances. The effect was especially pronounced in the presence of citric acid. While these observations have been confirmed by other investigators,[4,5,6] the site of action of insulin in this experimental system is unknown, although Krebs and Eggleston concluded that their evidence "suggests that insulin acts as a catalyst in the citric acid cycle."

It seemed possible to us that information in regard to the action of insulin in this experimental system could be obtained by studying the respiration of a suspension of minced pigeon breast muscle during the period when the insulin effect is present.

TABLE I

THE EFFECT OF INSULIN ON AEROBIC PYRUVATE REMOVAL

Two flasks contained 2.5 gm of minced pigeon breast muscle in 22.5 ml of calcium-free phosphate saline (pH 7.4) + 5.0 ml boiled muscle extract. One flask (enzyme A) received 1.5 ml phosphate buffer; the other (enzyme B), 1.5 mgm zinc-free insulin in 1.5 ml phosphate buffer. Both vessels were gassed with 100 per cent. O_2. 4.0 ml samples from each flask were placed in Warburg vessels, gassed with 100 per cent. O_2 and shaken at 40° C. until these pilot vessels showed the beginning of the insulin effect (ca. 80 minutes). The reserve flasks which had been shaken at 40° during this time were removed from the water bath and 4 ml of the enzyme suspensions + other additions were added to Warburg vessels as indicated in the table. The vessels were gassed with 100 per cent. O_2, equilibrated at 40° C. for 10 minutes, and substrates tipped in from the side arm. 20 per cent. KOH was placed in the center cup. Total volume of liquid: 4.7 ml. Experimental period, 25 minutes. Pyruvic acid was measured by the carboxylase method.

Experiment:	1		2		3	
Vessel:	1	2	1	2	1	2
Enzyme A (ml.)	4.0	....	4.0	....	4.0	....
Enzyme B (ml.)*	....	4.0	....	4.0	....	4.0
Pyruvate added (µl.)	431	431	373	373	393	393
Pyruvate utilized (µl.)	91.5	234.0	69	191	224	300
O_2 uptake (µl.)	390	475	441	475	634	944

* 1.1 units of insulin per ml.

In experiments to this end, we have found, first, that the greater oxygen uptake of a suspension of

TABLE II

EFFECT OF INSULIN ON THE O_2 UPTAKE AND PYRUVATE REMOVAL IN MALONATE-POISONED SYSTEMS

All manipulations are the same as those recorded in Table I. Malonate added to the vessel directly. The vessels were run for 70 minutes. The data in this table are from the same tissue suspension used in Experiment 2, Table I.

	Vessel									
	1	2	3	4	5	6	7	8	9	10
Enzyme A added (ml)	4.0	.....	4.0	.....	4.0	.....	4.0	.....	4.0	.....
Enzyme B added (ml)*	.....	4.0	.....	4.0	.....	4.0	.....	4.0	.....	4.0
Malonate conc. (M)	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019
Fumarate added (µl)	.....	.....	224	224	.....	.....	.....	.....	.....	.....
Oxaloacetate added (µl)	.....	.....	.....	.....	224	224	.....	.....	.....	.....
Citrate added (µl)	.....	.....	.....	.....	.....	.....	448	448	.....	.....
α-Ketoglutarate added (µl)	.....	.....	.....	.....	.....	.....	.....	.....	448	448
Pyruvate added (µl)	373	373	373	373	373	373	.....	.....	.....	.....
Pyruvate recovered (µl)	275	246	235	167	360	311	.....	.....	.....	.....
Pyruvate utilized (µl)	98	127	138	206	†	†	.....	.....	.....	.....
O_2 uptake (µl)	159	194	272	452	222	282	183	192	164	154

* 1.1 units of insulin per ml.

† Calculation of pyruvate utilization in the presence of oxaloacetate is impossible since oxaloacetate yields 2 mols CO_2 in the carboxylase method and is also decarboxylated to an unknown degree when added to tissues. These data, however, indicate an increased pyruvate uptake in the presence of insulin and oxaloacetate.

[1] This investigation was supported in part by a grant from Armour and Company.

[2] The work reported here was done by Lester Rice in partial fulfilment of requirements for a Ph.D. in biochemistry, Division of Biological Sciences, University of Chicago.

[3] H. A. Krebs and L. V. Eggleston, *Biochem. Jour.*, 32: 913, 1938.

[4] E. Shorr and S. B. Barker, *Biochem. Jour.*, 33: 1798, 1939.

[5] F. J. Stare and C. A. Baumann, *Cold Spring Harbor Symposia on Quantitative Biology*, 7: 1939.

[6] W. C. Stadie, John A. Zapp, Jr., and F. D. W. Lukens, *Jour. Biol. Chem.*, 132: 411, 1940.

pigeon breast muscle to which insulin had been added (as compared to a control maintained under the same conditions for a similar period of time) is accompanied by an increased ability to utilize pyruvic acid (Table I).

We have found, further, that this pyruvate utilization can be inhibited by malonate and restored, as Krebs and Eggleston have demonstrated in the case of fresh suspensions of pigeon muscle,[7] by the addition of fumarate + pyruvate and of pyruvate + oxaloacetate. While both of these reactions occur at a greater rate in the insulin-supplemented tissue, the rates of citrate and α-ketoglutarate oxidation are unaffected by the presence of the hormone (Table II).

These data demonstrate for the first time a direct *in vitro* association between the action of insulin and the oxidation of a carbohydrate substrate, namely, pyruvic acid. They suggest further that insulin is concerned in maintaining the functional integrity of either one or both of the enzyme systems involved in the reactions of fumaric and pyruvic acid or of oxaloacetic and pyruvic acid.

These experiments will be reported in greater detail elsewhere.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

ISOLATION OF AN ACTIVE SUBSTANCE FROM CALONYCTION ACULEATUM CAPABLE OF COAGULATING CASTILLA LATEX

CASTILLA latex is different from Hevea latex in that it is not easily coagulated by common chemical reagents. For many years, a juice prepared by natives of Central America from the moonvine of Nacta vine (*Calonyction aculeatum* formerly *Ipomea bona-nox*) has been used to coagulate the latex tapped from the Castilla tree. The origin of this discovery is apparently unknown. With increased interest in Castilla rubber resulting from the present rubber emergency, it has been necessary to seek some method for coagulating Castilla latex on a commercial scale. Trafton[1] has devised a method by which the latex is creamed, washed and finally coagulated with chemicals, but the method requires that the pH of the latex be rather rigidly controlled during processing, a condition not always attainable under field conditions, particularly when native labor is used. The native method of coagulation with Nacta extract would continue to be reasonably satisfactory except for two problems: (1) The vine has been almost completely exterminated in its former habitats, where it was associated with Castilla trees, and (2) there are areas in which moonvine has never been found in association with Castilla. Hence, the desirability of isolating the active principle from Nacta vine has been suggested as offering a method whereby a dried extract or some other suitable concentrate might be prepared in one area to be shipped to some other area where Castilla latex is to be coagulated. As the following directions will indicate, this laboratory has been successful in isolating from Nacta a material which is very active in coagulating Castilla latex under laboratory conditions.

METHODS AND MATERIALS

Calonyction aculeatum grows abundantly in southern Florida. It has been possible, therefore, to have ample material shipped in from this source so as to arrive in optimum condition (material shipped from Mexico decayed in transit). Preliminary experiments indicated that no loss in activity was experienced when the vine was rapidly dried *in vacuo* at 70° C; similarly, it was found that the substance responsible for coagulating Castilla latex was not soluble in water, but was readily soluble in ethyl alcohol, acetone, ethyl ether, petroleum ether and benzene. With these facts in mind, the following procedure was adopted in preparing an active material.

Ten grams of dry stems of *C. aculeatum*, ground to pass 40 mesh, were extracted with ethyl ether for 12 hours in a Soxhlet apparatus. At the expiration of this period, the green ether extract was transferred to an evaporating dish and the ether removed, leaving a sticky mass of material heavily charged with chlorophyll. This was then dissolved in a small quantity of benzene, transferred to a beaker and activated charcoal added. The material was heated on a steam bath for about ten minutes to insure adequate adsorption. Filtration of the benzene extract to which charcoal had been added disclosed a yellow-colored filtrate from which most, if not all, of the photosynthetic pigments had been removed by adsorption on carbon. The filtrate was evaporated to dryness leaving a resinous mass of yellow color. This material was dissolved in a small quantity of acetone and then dispersed into approximately 30 ml of water, producing a white, cloudy, colloidal sol which, when viewed by reflected light, appeared to have a reddish tinge. The acetone was removed from the sol by warming on a steam

[7] H. A. Krebs and L. V. Eggleston, *Biochem. Jour.*, 34: 442, 1940.

[1] Unpublished data.

bath until the odor of acetone could no longer be detected. The hydrosol was cooled in an ice bath to about 5° C. Upon standing overnight in an ice chest, a yellow substance separated from the sol. When subsequently centrifuged at 4,500 RPM for 15 minutes, all the material was precipitated, leaving a clear supernatant liquid. The precipitated material was washed several times with water, the water decanted, the precipitate redissolved in acetone, filtered, redispersed into water, and the acetone removed as before. Centrifuging caused a clear, yellow, resin-like substance to collect at the bottom of the centrifuge tube. The resin was gathered on a stirring rod and removed from the tube for drying. From ten grams of dry plant material, 400 milligrams of dried resin were obtained, or a yield of about 4 per cent. on a dry weight basis.

Coagulation Tests of Calonyction Resin with Castilla Latex

The Castilla latex used in the following experiments was received from Mexico and labeled "Latex Castilla por de Pichucalco," and was collected on September 15, 1942. The shipment arrived in Washington on October 14, 1942, in apparently good condition. Ten milliliters of undiluted latex were measured in a graduate, poured into a 30 ml beaker and the desired amount of sol added for coagulative tests. The beakers were kept covered to diminish surface oxidation of the latex during the time of the test. When coagulation occurred, the rubber was separated from the serum at the end of 14 hours, washed several times in water, and weighed after being superficially dried in a low temperature oven. In some cases, the serum also was evaporated to dryness for rubber content determination. Resin and rubber analyses were made by the Bailey-Walker method using acetone and benzene as solvents for resins and rubber, respectively.

A sol containing 0.82 mg of resin per milliliter of water, and another sol containing 0.47 mg of resin per milliliter were prepared by first dissolving the resin in a small amount of acetone, dispersing the resin into water with stirring, removing all the acetone by warming, and then making the sol to a known volume with water. Tables I and II illustrate the coagulating powers of these sols, and the composition of the coagulum and serum.

TABLE I

Coagulative Power of a Calonyction Resin Sol Containing 0.47 mg of Resin Per Milliliter of Water. Ten Milliliters of Latex Used in All Tests

Ml of sol	Mg of nacta resin	Time of coagulation	Weight of rubber in grams
1.0	0.47	None in 12 hours	0
2.0	0.94	None in 12 hours	0
4.0	1.88	Begins in 30 minutes	2.35
8.0	3.75	Begins in 10 minutes	2.95
16.0	7.52	Begins almost at once	2.68

TABLE II

Coagulative Power of a Calonyction Resin Sol Containing 0.82 mg of Resin Per Milliliter of Water. Ten Milliliters of Latex Used in All Tests

Ml of sol	Mg of nacta resin	Time of coagulation	Per cent. rubber coagulated	Coagulum			Serum	
				Weight in grams	Per cent. resins	Per cent. rubber	Weight in grams	Per cent. rubber
0.5	0.41	None in 14 hours	0	0	...	....	10.32	...
1.0	0.82	None in 14 hours	0	0	...	....	10.32	...
2.0	1.64	10 minutes ±	20.7	2.14	5.60	72.34	8.18	5.63
4.0	3.28	5 minutes ±	23.3	2.41	6.37	58.27*	7.91	1.78
8.0	6.56	2 minutes ±	23.4	2.42	7.07	76.60	7.90	0.78

* Benzene extraction of rubber not complete after 32 hours.

These data are suggestive of the use that this resin may find in the commercial production of Castilla rubber. Since, however, absolutely fresh latex has been unavailable, we are hesitant in predicting the coagulative powers of Nacta resin under field conditions, and for this reason, we are withholding comment and interpretation of the data contained in the tables until the results of further trials on fresh latices have been ascertained.

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BOOKS RECEIVED

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